

In the Claims

Please amend the claims presented during the international phase as follows.

Applicant presents a full set of claims showing markups of the claims with insertions and deletions indicated by underlining (or double bracketing) and strikethrough text, respectively.

1. (Original) An anti-IFN-gamma polypeptide comprising at least one anti-IFN-gamma single domain antibody.
2. (Original) An anti-IFN-gamma polypeptide according to claim 1, wherein at least one anti-IFN-gamma single domain antibody, is a *Camelidae* VHH antibody.
3. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claim 1 claims-1 and-2~~ wherein at least one single domain antibody corresponds to a sequence represented by any of SEQ ID NOs: 1 to 35.
4. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claim 1 any of claims-1 to-3~~ further comprising at least one single domain antibody directed against a serum protein.
5. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claims~~ claim 4 wherein ~~a~~ the serum protein is any of serum albumin, serum immunoglobulins, thyroxine-binding protein, ~~transferring~~ transferrin, or fibrinogen.
6. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claim 4 claims-4 and-5~~ wherein ~~an~~ the anti-serum protein single domain antibody correspond to a sequence represented by any of SEQ ID NOs: 36 to 39 and 62 to 74.
7. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claim 4 any of claims-4 to-6~~ corresponding to a sequence represented by any of SEQ ID NOs: 40 to 42.
8. (Currently amended) An anti-IFN-gamma polypeptide according to ~~claim 1 any of claims-1 to-6~~ further comprising at least one single domain antibody selected from the group

consisting of anti-TNF-alpha single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody.

9. (Currently amended) An anti-IFN-gamma polypeptide according to claim 1 any of claims 1 to 7, wherein the number of single domain antibodies directed against IFN-gamma is at least two.

10. (Original) An anti-IFN-gamma polypeptide according to claim 9 corresponding to a sequence represented by any of SEQ ID NOS: 59 to 61.

11. (Currently amended) An anti-IFN-gamma polypeptide according to claim 1 any of claims 1 to 10, wherein at least one single domain antibody is a humanized *Camelidae* VHVs.

12. (Currently amended) A composition comprising an anti-IFN-gamma polypeptide according to claim 1 any of claims 1 to 11 together with at least one single domain antibody from the group consisting of anti-TNF-alpha single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody, for simultaneous, separate or sequential administration to a subject.

13. (Currently amended) An anti-IFN-gamma polypeptide according to claim 8 any of claims 7 to 11, or a composition according to claim 12 wherein at least one anti-TNF-alpha single domain antibody correspond to a sequence represented by any of SEQ ID NOS: 43 to 58.

14.-15. (Canceled)

16. (Currently amended) An anti-IFN-gamma polypeptide according to claim 4 any of claim 1 to 11, and 13 to 15, or a composition according to claims 12 to 15 wherein said single domain antibodies are *Camelidae* VHVs.

17. (Currently amended) A nucleic acid encoding an anti-IFN-gamma polypeptide according to claim 1 any of claims 1 to 16.

18. (Currently amended) A method of identifying an agent that modulates the binding of an anti-IFN-gamma polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ to IFN-gamma comprising the steps of:

- (a) contacting an anti-IFN-gamma polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is IFN-gamma, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies identified said candidate modulator as an agent that modulates the binding of an anti-IFN-gamma polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ and IFN-gamma.

19. (Currently amended) A method of identifying an agent that modulates IFN-gamma-mediated disorders through the binding of an anti-IFN-gamma polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ to IFN-gamma comprising:

- (a) contacting an anti-IFN-gamma polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is IFN-gamma, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies identified, said candidate modulator as an agent that modulates IFN-gamma-mediated disorders.

20. (Currently amended) A method of identifying an agent that modulates the binding of IFN-gamma to its receptor through the binding of an anti-IFN-gamma polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ to IFN-gamma comprising:

- (a) contacting an anti-IFN-gamma polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is IFN-gamma, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the

binding in the absence of said candidate modulator, identifies identified said candidate modulator as an agent that modulates the binding of IFN-gamma to its receptor.

21. (Currently amended) A kit for screening for agents that modulate IFN-gamma-mediated disorders comprising an anti-IFN-gamma polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ and IFN-gamma.

22.-25. (Canceled)

26. (Currently amended) A method for treating and/or preventing and/or alleviating disorders relating to inflammatory reactions comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a nucleic acid according to claim 17, or a composition according to any of claims 12 to 16, or an agent according to any of claims 20 to 21 for the preparation of a medicament for treating and/or preventing and/or alleviating disorders relating to inflammatory reactions.

27. (Canceled)

28. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of an IFN-gamma modulating polypeptide comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulating polypeptide that is able pass that passes through the gastric environment without being inactivated.

29. (Canceled)

30. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of an IFN-gamma modulating polypeptide comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a

~~composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulator to the vaginal and/or rectal tract.~~

31. (Canceled)

32. (Currently amended) ~~A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of a therapeutic compound to the upper respiratory tract and lung comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring the delivery of a therapeutic compound to the upper respiratory tract and lung.~~

33. (Canceled)

34. (Currently amended) ~~A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulator comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulator, wherein said disorder increases the permeability of the intestinal mucosa.~~

35. (Canceled)

36. (Currently amended) ~~A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulator comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring delivery of a IFN-gamma modulator that is able pass that passes through the tissues beneath the tongue.~~

37. (Canceled)

38. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders requiring the delivery of a IFN-gamma modulator comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring delivery of a IFN-gamma modulator that is able pass that passes through the skin.

39. (Currently amended) A method according to claim 19, a kit according to claim 21, a nucleic acid or agent according to claim 25, use of a nucleic acid or agent according to claim 26, a composition according to any of claims 25, 27, 29, 31, 33, 35, 37 and 39, use of a composition according to any of claims 26, 28, 30, 32, 34, 36, and 38, an anti-IFN-gamma polypeptide of any of claims 25, 27, 29, 31, 33, 35, 37 and 39, use of an anti-IFN-gamma polypeptide according to any of claims 26, 28, 30, 32, 34, 36, and 38 wherein said disorders are any of inflammation, rheumatoid arthritis, Crohn's disease, ulcerative colitis, inflammatory bowel syndrome, multiple sclerosis, Addison's disease, Autoimmune hepatitis, Autoimmune parotitis, Diabetes Type I, Epididymitis, Glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, Hemolytic anemia, Systemic lupus erythematosus, Male infertility, Multiple sclerosis, Myasthenia Gravis, Pemphigus, Psoriasis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Scleroderma, Sjogren's syndrome, Spondyloarthropathies, Thyroiditis, and Vasculitis.

40. (Currently amended) A composition comprising a nucleic acid or agent according to claim 25, an the anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11 and 13 to 16, or a composition according to any of claims 12 to 16, and a suitable pharmaceutical vehicle.

41. (Currently amended) A method of diagnosing a disorder characterised by the dysfunction of IFN-gamma comprising:

- (a) contacting a sample with an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16,
- (b) detecting binding of said polypeptide to said sample, and

(c) comparing the binding detected in step (b) with a standard, wherein a difference in binding relative to said sample is diagnostic of a disorder characterised by dysfunction of IFN-gamma.

42.-43. (Canceled)

44. (Currently amended) A method for purification of IFN-gamma, comprising contacting a sample with the Use of an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 for the purification of said IFN-gamma.

45. (Currently amended) A method Use of an anti-IFN-gamma polypeptide of any of claims 1 to 11, and 13 to 16 for inhibiting the interaction between IFN-gamma and one or more IFN-gamma receptors, comprising contacting IFN-gamma with the anti-TNF-alpha polypeptide of claim 1.

46. (Currently amended) A method for producing an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 comprising the steps of:

- (a) obtaining double stranded DNA encoding a *Camelidae* VHH directed to IFN-gamma,
- (b) cloning and expressing the DNA selected in step (b).

47. (Currently amended) A method of producing an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 comprising:

- (a) culturing host cells comprising nucleic acid capable of encoding that encode an anti-IFN-gamma polypeptide of claim 1 any of claims 1 to 11, and 13 to 16, under conditions allowing the expression of the polypeptide, and,
- (b) recovering the produced polypeptide from the culture.

48. (Original) A method according to claim 47, wherein said host cells are bacterial or yeast.

49. (Canceled)